REMARKS

Claims 1-3, 7-11, 14, 16-20, 26-29, 36-38, and 40 are rejected.

Sequence Rules

The Examiner states the current case fails to meet sequence rules outlined in 37 C.F.R. § 1.821-1.825. In particular, there are sequences on page 38 and 41-43 which are present but which are not associated with SEQ ID numbers. Also, the paper copy and CRF submitted only includes SEQ ID NOS:1-7 and do not include SEQ ID NOS:8-13 and therefore, fail to include the elected species.

Applicants are herein submitting a new CFR and paper copy of the sequence listing, which include SEQ ID NOS: 8-13 and additional SEQ ID NOS, thus alleviating this rejection.

Specification

The Examiner has objected to the disclosure because of the following formalities: the disclosure is objected to because it contains an embedded hyperlink and/or form of browser-executable code (see page 7 of specification, for example). The Examiner states Applicant is required to delete the embedded-hyperlink and/or other form of browser-executable code.

Applicants have removed the embedded hyperlinks and/or other form of browser-executable codes throughout the specification by removing the underling from the URLs, thus alleviating this rejection.

Claim Rejections - 35 U.S.C. § 112

Claims 1-3, 7-11, 14, 16-20, 26-29, 36-38 and 40 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner states all of the current claims encompass a genus of nucleic acids which comprise prolactin receptor polymorphisms which are not disclosed in the specification. The genus includes an enormous number of polymorphisms for which no written description is provided in the specification.

Applicants have amended claims to show they had possession of the claimed invention. Specifically, Applicants have amended claim 1 by describing the claimed invention using the descriptive means of the structure (SEQ ID) of the prolactin receptor gene and function. Dependent claims from claim 1 by virtue of their dependency contain all the limitations of amended claim 1. Moreover, Applicants claims recite primer sequences that amplify a specific region of the gene containing the polymorphism, thus allowing for the selection of a sequence having a polymorphism.

Also, claim 36 has been amended to recite the structure of the prolactin receptor gene.

The current Guidelines for Examination of Patent Applications under the 35 USC 112, ¶1, "Written Description" Requirement, states that examples of identifying characteristics for biomolecules, such as nucleic acids, are unique cleavage by particular enzymes and detailed restriction enzyme maps.

Applicants respectfully submit they have shown possession to this genus as Applicants have disclosed and claimed that the presence or absence of a marker in the genus may be assayed by PCR-RFLP analysis using restriction endonucleases, which cleaves the sequence at a specific, unique site. One or more additional restriction enzymes may be used. These additional enzymes can be determined by routine experimentation and the teachings, incorporated by reference in the specification by one of ordinary skill in the art.

As disclosed and claimed, the method of Applicants' invention exposes the gene to a restriction enzyme that yields restriction fragments of the gene of varying length, separating the restriction fragments to form a restriction pattern, then comparing the resulting restriction fragment pattern from an animal's prolactin receptor gene that is either known to have or not have the desired marker. (See spec. page 6, lines 3-5). Since a restriction map is a description of restriction endonuclease cleavage sites within a piece of nucleic acid, such as DNA, one of ordinary skill in this art would be able to use the methods of Applicants' invention to make a restriction map of the prolactin receptor gene sequence as set forth in SEQ ID NO: 3 upon the use of any restriction enzyme which goes on to show a restriction pattern that has what would be a desired marker. Applicants have disclosed in the Figures and claimed the expected band sizes for a polymorphism and would be able to do so with routine experimentation for any polymorphism found on or within the prolactin receptor gene. (See claim 40 and newly added claims 41-53).

Thus, Applicants have shown possession by the following relevant identifying characteristics: the structure of the gene, unique cleavage by particular enzymes, and restriction enzyme patterns from which a restriction enzyme map can be generated, without undue experimentation.

Applicants respectfully submit they should be entitled to any nucleic acid having the sequence set forth in SEQ ID NO:3 or at the very least any region thereof which can be defined by primers capable of amplifying a region of the gene having a polymorphism found to be associated with increased litter size.

The Examiner also states that in narrow claims such as claim 7, where Mse1 is required, no specific polymorphism is named.

Applicants respectfully wish to bring to the attention of the Examiner that on page 7, lines 12-14 of the Written Description, Applicants disclose that "the designation of a particular polymorphism is made by the name of a particular restriction enzyme." Therefore, Applicants, in claim 7, for example, have named the specific polymorphism by stating the particular restriction enzyme. Moreover, Applicants have amended the specification by adding SEQ ID NOS to the sequences.

Claim Rejections - 35 U.S.C. § 112

Claims 1-3, 7-11, 14, 16-20, 26-29, 36-38 and 40 were rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for some polymorphisms in the porcine prolactin receptor such as the Alu polymorphism, does not reasonably provide enablement for all polymorphism including the MseI polymorphism. The Examiner further states that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner states the claims are broadly drawn to encompass a method of screening for any polymorphism in the prolactin receptor gene. Even the narrow claim 7 is drawn to any polymorphism which is detected by the use of the Mse1 restriction enzyme. The method broadly encompasses the use of a method in any type of mammalian patient. Further, the animals undergoing the screening may contain any of a number of complicating variables, since the background genotype with regard to other genes may play significant roles in the effect on litter sizes.

Applicants have amended the claims to recite an animal possessing a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:3 or a fragment thereof.

Applicants disclose on page 7 of the specification, line 26-29, that due to the highly conserved nature of the prolactin receptor gene, it is expected that other animals will demonstrate polymorphisms in this gene or a region thereof which are analogous to those disclosed and claimed which can be determined by sequence homology or similar protein effects. Methods such as PCR and hybridization, which are well known in this art, can be used to identify sequences having substantial sequence similarity to the sequence of the invention without undue experimentation. Hybridization conditions would enable one skilled in the art to detect a polynucleotide having at least 95% sequence identity because such conditions would reasonably ensure having high complementarity to SEQ ID NO:3 and its naturally occurring variants.

The Examiner states the quantity of experimentation in this area is very large since there is significant variability in the effects of polymorphisms on phenotypes such as litter size. Screening each possible polymorphism in the prolactin receptor gene represents an inventive, unpredictable and difficult undertaking in itself. As shown on page 46 in the results, over 1500 litters were analyzed involving literally hundreds of pigs. The Examiner states this would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not provide any guarantee of success in the succeeding steps.

Applicants traverse this rejection. This test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction on which the experimentation should proceed. *In re Wands*, 853 F.2d at 737, 8 U.S.P.Q.2d at 1404 (*citing In re Angstadt,* 537 F.2d 489, 502-04, 190 U.S.P.Q. 214, 218 (CCPA 1976)). The instant disclosure is enabling for the screening of other possible polymorphisms in the prolactin receptor gene because it would take no more than routine screening to identify the presence of

the polymorphism in the gene since methods, such as those disclosed on page 10, lines 14-15, are well known to those with ordinary skill in this art. Moreover, Applicants disclose starting at page 10 a general overview of techniques which can be used to assay for a polymorphism in this gene. Additionally, the types of mutations suggested by the disclosure are conventional and one skilled in the art could easily screen for such mutants using conventional genetic engineering methods, therefore the specification is enabling.

The Unpredictability of the Art and the State Of The Art

The Examiner states the specification demonstrates the unpredictability of this invention since the P values identified by the specification for the association of the MseI SNP with litter size are 0.2 and 0.3. The Examiner concludes that by scientific convention, the data presented for the MseI SNP on page 46 of the specification fails to demonstrate a statistically significant effect. It is highly unpredictable whether the SNP is, in fact, associated with the increased litter size. Unlike the AluI polymorphisms, shown on page 36, where there is a P value below 9.95, the MseI polymorphisms fails to show a significant effect. The factor of unpredictability weighs against the enablement of the claims.

Applicants traverse this rejection. The failure to produce a significant association as a single test does not mean that a polymorphism is not useful in an analysis of the gene and trait associations. Besides, there is an indication of an effect of MseI on TNB (total number born). With MseI, the preferred allele, allele 2, the effect may have both additive and dominance components. While the effect is not statistically significant for NBA (number born alive), however, the trend is in the same direction and the failure to reach significance may simply reflect the unequal genotype frequencies and the combination of lower mean values and higher standard errors for this trait in this dataset.

Guidance in the Specification

The Examiner states "the specification, while suggesting an association between the Mse1 SNP and litter size, did not provide sufficient evidence to demonstrate the association."

Applicants traverse this rejection. Looking at the application as a whole, the evidence provided by Applicants need not be conclusive but merely convincing to one skilled in the art. Therefore, Applicants respectfully submit that from the specification, one of ordinary skill would not only be convinced that there is an association between MseI SNP and litter size, but also that that this identification of this association would be useful in an analysis of gene and trait associations. Therefore, Applicants respectfully request Examiner to withdraw this rejection.

Double-Patenting

Claims 1-3, 8-11, 16-20, 26-29, 36-38 and 40 were rejected under the judicially created doctrine of obviousness-type double-patenting as being unpatentable over claim 3 of U.S. Patent No. 5,935,784 in view of Rothschild et al. (U.S. Patent 5,374,526).

Therefore, the Examiner concludes, it would have been *prima facia* obvious to one having ordinary skill in the art at the time the invention was made to combine claim 3 of the '784 patent with the methods and genes of Rothschild since Rothschild states "thus, the markers will be selection tools in breeding programs to develop lines and breeds that produce litters containing a large number of offspring (column 2, lines 55-57)".

Applicants are herein submitting a Terminal Disclaimer, which disclaims any term of the patent issuing from this application, which would extend beyond the term of Patent No. 5,935,784. Applicant respectfully request Examiner to withdraw this rejection.

Conclusion

Reconsideration and allowance is respectfully requested. Pursuant to 37 CFR § 1.16(c), for a large entity, please charge deposit account number 26-0084 in the amount of $270.00, to cover the cost of the adding claims 41-55 after the filing fee. Charge any overpayments or deficiencies to Deposit Account No. 26-0084.

Please charge Deposit Account No. 26-0084 the amount of $410.00 for a two-month extension of time. No other fees are believed to be due in connection with this amendment; however, consider this a request for any inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Respectfully submitted,

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